REMARKS

Claims 1-27 are pending.

Claim Rejections - 35 U.S.C. § 103(a)

Applicants respectfully traverse the obviousness rejection of claims 1-27 over Ott *et al.* (GB 2,114,978) taken with Tomita *et al.* (US 4,032,404), Venek *et al.* ("Selection and Accumulation in Open Systems" in Overproduction of Microbial Metabolites, ed. by Z. Vanek and Z. Hostalek, 1986, pp. 191-195), BG 50996 and McIntyre (Biotechnology and Bioengineering, (1996) vol. 49, pp. 412-420.

Ott *et al.*discloses a batch-mode fermentation process for producing 6'-O-carbamoyl tobramycin by incubating a nutritive medium containing a 6'-O-carbamoyl tobramycin producing strain MNG204 of *Streptomyces tenebrarius*, and organic carbon and nitrogen sources in a submerged, aerated culture in a shaker until a substantial amount of 6'-O-carbamoyl tobramycin is accumulated (page 2, lines 27-38; page 3, lines 4, 5 and 14; page 4, line 15).

Tomita *et al.*discloses a fermentation process for producing 6'-O-carbamoyl tobramycin by culturing a strain of 6'-O-carbamoyl tobramycin producing *Streptoalloteichus hindustanus* in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen (column 10, line 64 to column 11, line 5 and column 11, lines 32-37).

Ott *et al.*and Tomita *et al.* differ from claims 1-27 at least in not teaching or suggesting regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth the 6'-O-carbamoyl tobramycin producing microorganism, an assimilable

carbon source and an assimilable nitrogen source. The Office Action attempts to rely on Vanek *et al.*, BG 50996 and McIntyre to cure this deficiency.

The Office Action relies on Vanek *et al* .for the teaching that regulating constant levels of carbon and nitrogen sources by using a continuous culturing process using chemostats was known in the prior art. Applicants respectfully disagree.

Vanek *et al.* does not suggest regulating constant levels of the assimilable carbon source and assimilable nitrogen source in a fermentation broth containing a 6'-O-carbamoyl tobramycin producing microorganism, an assimilable carbon source and an assimilable nitrogen source. Applicants note that Vanek *et al.* merely teaches using chemostats to select and enrich certain mutants of the microorganism growing in a fermentation medium (please see the section title, "IV. Selection and Accumulation in Open Systems" in page 191; page 191, the last two paragraphs; page 192, the 2nd to 4th full paragraphs; page 195, the first 3 paragraphs). But Ott *et al.* and Tomita *et al.* do not teach or suggest the desirability of enriching certain mutants of the microorganism growing in a fermentation medium. Thus, there was no suggestion or motivation to modify the process of Ott *et al.* or Tomita *et al.* by using a chemostat of Vanek *et al.* to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation broth used in the process of Ott *et al.* or Tomita *et al.*

The Office Action also attempts to rely on BG 50996 and McIntyre to cure the deficiencies of Ott *et al.* and Tomita *et al.* The Office Action states that "the Bulgarian patent '996 and McIntyre et al. adequately demonstrate the use of regulation of carbon and nitrogen sources in the production of antibiotics with *Streptomyces*, respectively *S. tenebrarius* strains

using a constant glucose and nitrogen feed...". Applicants respectfully disagree.

The Office Action requests an English translation of BG 50996. Unfortunately, applicants do not have an English translation of BG 50996. The Examiner is urged to contact the technical library of USPTO to obtain a translation of BG 50996.

BG 50996 discloses the use of batch-mode feeding in the production of tobramycin. BG 50996 does not teach using continuous feeding in the production of tobramycin. The batch-mode feeding results in fluctuations of the substrate concentrations in the broth, which is not beneficial. The continuous feeding used in the claimed invention, in contrast, allows maintaining the broth substrate concentration in a narrow range even when there is metabolic change in the strain during the fermentation. So the continuous feeding used in the claimed invention allows a finely controlled fermentation. Another important difference is that BG 50996 adds a substrate mixture containing both carbon and nitrogen sources preventing maintaining the optimal concentrations of the carbon source and nitrogen source independently during the fermentation.

The sentence that mentions BG 50996 and the preceding sentence in page 14 of the instant specification, under Detailed Description of the Invention, are reproduced herein: "Accordingly, in addition to adjusting the internal pressure and aeration rate of the fermentation, a better demanded optimal value of 6'-O-carbamoyl tobramycin is achieved by continuously feeding assimilable carbon and carbon sources and inorganic phosphate. Accordingly, the advantages can be effected more easily using the continuous feeding relative to the batch-like feeding (See BG 50996 patent)." Page 14 of the instant specification does NOT state that BG 50996 teaches the advantages of regulating assimilable carbon and nitrogen sources in a

fermentation broth using continuously feeding in the production of 6'-O-carbamoyl tobramycin. Thus, BG 50996 does not provide any suggestion or motivation to modify the fermentation process of Ott et al or Tomita et al in the production of 6'-O-carbamoyl tobramycin by regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth containing the 6'-O-carbamoyl tobramycin producing microorganism, an assimilable carbon source and an assimilable nitrogen source.

The Office Action cites the paragraph bridging the left and right columns in page 2 and Fig. 5 of McIntyre. However, the paragraph bridging the left and right columns in page 2 of McIntyre merely discloses the general procedures for incubation of production flasks, and is silent on regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth containing the 6'-O-carbamoyl tobramycin producing microorganism, an assimilable carbon source and an assimilable nitrogen source.

Fig. 5 of McIntyre shows the production rate of vancomycin by *Amycolatopsis orientalis* cultures fed one of 5 constant input rates of glucose. Fig. 5 of McIntyre differs from the claimed invention in several regards.

First, Fig. 5 of McIntyre does not teach regulating a constant level of assimilable nitrogen source in the fermentation broth. The experiment conducted in Fig. 5 of McIntyre only fed a constant rate of glucose into the culture medium, and was silent on regulating a constant level of assimilable nitrogen source. Even if the person of ordinary skill in the art were to use the disclosures of McIntyre to modify the fermentation process of 6'-O-carbamoyl tobramycin production according to Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.* and BG 50996,

the person would not arrive at the process of claim 1. This is one of the reasons why the instant claims should not have been rejected as obvious over Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre.

Second, even if *arguendo* one were to assume that following the continuous culture process of Fig. 5 of McIntyre would regulate a constant level of assimilable nitrogen source, Fig. 5 of McIntyre shows the production of **vancomycin, not 6'-O-carbamoyl tobramycin**. McIntyre admits that the physiological regulation and control of the production of antibiotics in *Streptomyces* is poorly understood (see p. 412, right column, the first sentence of the first full paragraph). The production of antibiotics by microorganisms is not reasonably predictable because antibiotic production does not always occur once the growth rate has declined as a consequence of nutrient limitation, and several examples of antibiotics produced during exponential growth have been reported (McIntyre, p. 412, right column, second and third sentences of the first full paragraph). There is no reasonable expectation that applying the teachings of McIntyre on the production of **vancomycin** using a continuous culture process to modify the processes of Ott et al and Tomita et al would improve the production of another antibiotic, namely **6'-O-carbamoyl tobramycin**, compared with the batch-like processes of Ott et al and Tomita et al. However, for a modification of a prior art process to be *prima facie* obvious, a reasonable expectation of success is required. See *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991). This is one of the reasons why the instant claims should not have been rejected as obvious over Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre.

Another reason why claims 1-27 would not have been *prima facie* obvious over Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre is that the prior art does not teach that modifying the process of Ott *et al.* or Tomita *et al.* by using the chemostat of Vanek *et al.* or the continuous culture processes of BG 50996 or McIntyre to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation broth would result in an **improved yield** of the 6'-O-carbamoyl tobramycin as required by step b) of claim 1. There was no reasonable expectation of success (improved yield of the 6'-O-carbamoyl tobramycin) if one of ordinary skill in the art were to modify the process of Ott *et al.* or Tomita *et al.* by using the chemostat of Vanek *et al.* or the continuous culture processes of BG 50996 or McIntyre to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation broth. There is no *prima facie* obviousness when the modification of the prior art as alleged by the Examiner to arrive at the claimed invention has no reasonable expectation of success. See MPEP 2143.02.

Applicants note that McIntyre discloses that "[d]espite the potential of increased volumetric productivity compared to batch culture, continuous culture processes have not been employed in commercial antibiotic production, primarily as a result of strain degeneration leading to lower productivity" (see p. 412, right column, second full paragraph, second sentence). McIntyre also discloses that "**[d]ecreases** in antibiotic production under various nutrient and growth conditions in continuous culture studies have **frequently** been reported for *Streptomyces*" (p. 418, left column, first full paragraph, second sentence; emphasis added). Thus, McIntyre's disclosures **teach away** from modifying the 6'-O-carbamoyl tobramycin production processes of

Ott et al and Tomita et al using continuous culture procedures. This is another reason why the instant claims should not have been rejected as obvious over Ott *et al.* taken together with Tomita *et al.,* Vanek *et al.,* BG 50996 and McIntyre.

McIntyre teaches the use of the continuous culture procedure as **a means of researching** the relationship between the physiological status of an organism and the production of antibiotics under steady-state culture conditions (see p. 412, right column, second full paragraph, the third sentence; emphasis added). There would have been no motivation to modify a prior art substance if the prior art does not teach any specific or significant utility for the prior art substance. *See In re Stemniski*, 170 USPQ 343 (CCPA 1971); *In re Lalu*, 223 USPQ 1257 (Fed. Cir. 1984). According to MPEP 2107.01, carrying out further research to identify or reasonably confirm a "real world" context of use is not "substantial utility." Thus, there would have been no motivation to apply the continuous culture procedure taught by McIntyre as a means of research in the processes of Ott et al and Tomita et al. This is another reason why the instant claims should not have been rejected as obvious over Ott *et al.* taken together with Tomita *et al.,* Vanek *et al.,* BG 50996 and McIntyre.

As a result, claims 1-27 would not have been *prima facie* obvious over Ott *et al.* taken together with Tomita *et al.*, Vanek *et al.,* BG 50996 and McIntyre.

A further reason why claims 1-27 would not have been obvious over Ott et al. taken together with Tomita et al., Vanek et al., BG 50996 and McIntyre, is that the improved yields of the 6'-O-carbamoyl tobramycin achieved by regulating constant levels of the assimilable carbon and nitrogen sources (please see Examples 4 and 5 in comparison with Examples 1-3) discovered

by the present inventors were unexpected results. The prior art does not teach or suggest that regulating constant levels of the assimilable carbon and nitrogen sources in a fermentation broth containing a 6'-O-carbamoyl tobramycin producing microorganism would result in improved yields of the 6'-O-carbamoyl tobramycin.

Withdrawal of the obviousness rejection is requested.

Conclusion

If the Examiner deems that there are issues that can be resolved by a telephone interview, the Examiner is urged to telephone the undersigned.

In the event that this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 11-0600, referencing the Attorney Docket No. 02664/47002.

Respectfully Submitted,

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